Materials and Methods

Study Population

The ARIC Study recruited a population-based cohort of 15,792 persons aged 45 to 64 years in 1987 through 1989, by list or area probability sampling, from Forsyth County, North Carolina; Jackson, Mississippi (African Americans only); the northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland.[1] ARIC performed a baseline examination of participants and followed them by annual telephone contact and up to four reexaminations in 1990-1992 (Visit 2), 1993-1995 (Visit 3), 1996-1998 (Visit 4), and 2011-2013 (Visit 5). We conducted follow-up for clinical AAAs after baseline and ascertained asymptomatic AAAs by an ultrasound examination at Visit 5. All participating institutions gave institutional review board approval for this study and all participants provided written informed consent.

Baseline (1987-89) Measurements

The baseline home interview and clinic examination measured various cardiovascular risk factors and conditions including anthropometric measures, smoking, alcohol intake, history of physician-diagnosed diabetes and other cardiovascular conditions, and medication use. ARIC staff took three blood pressure measures with a random-zero sphygmomanometer. The average of the last two measurements was included for analysis. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or taking antihypertensive medication within the past two weeks. Prevalent diabetes mellitus was defined as a fasting glucose level $\geq$ 126 mg/dL, nonfasting glucose level $\geq$ 200 mg/dL, a self-reported physician diagnosis of diabetes, or treatment for diabetes. Ankle-brachial index was computed by dividing the average of ankle SBP measurements by the average of brachial SBP measurements in a randomly selected leg; peripheral arterial disease (PAD) was defined as an ankle-brachial index <0.9 or intermittent claudication. After requesting participants fast at least 8 hours, blood samples were drawn from an antecubital vein. A central laboratory measured

plasma total cholesterol[2] and triglycerides[3] by enzymatic methods and calculated LDL cholesterol (LDL-C).[4] HDL cholesterol (HDL-C) was measured after dextran-magnesium precipitation of non-HDL lipoproteins.[5]

Measurement of Smoking Behavior at Baseline and Follow-up Exams

Information on smoking was obtained by interview at each of the five study visits and participants were classified as current, former, or never smokers. Pack-years of smoking were calculated as the average number of cigarettes smoked per day multiplied by the years of smoking divided by 20 (the number of cigarettes in a standard packet). We defined longitudinal smoking status based on smoking behavior ascertained from Visit 1 to Visit 4 (or Visit 3 if smoking information in Visit 4 was missing) as follows: Never smokers (defined as never smoker from Visit 1 to Visit 4), quitters before Visit 1 (former smoker at Visit 1 and not smoking at Visit 2 to Visit 4), recent quitters (current smoker at Visit 1 and non-smoker from Visit 2 to Visit 4), and continuous smokers (current smoker from Visit 1 through Visit 4 allowing for "former smoker" status only once between Visit 2 to Visit 4). Eighty-seven percent of participants who were not censored early had information on smoking up to Visit 4 and the other 13% up to Visit 3.

AAA Ascertainment

At the baseline examination in 1987-89, we collected information on history of prior arterial surgery and excluded participants reporting prior AAA surgery or aortic angioplasty from all analyses.

Incident, clinical AAAs were identified by searching hospitalization and death records as well as Medicare data. ARIC conducted annual telephone calls with participants to ask about any interim hospitalizations and identified deaths, and these records were obtained. ARIC also conducted surveillance of local hospitals to identify additional hospitalizations or deaths. We also linked participant identifiers with Medicare data from the Centers for Medicare and

Medicaid Services (CMS) for 1991-2011, to find additional hospital or outpatient events for those over 65 years. Clinical AAAs were defined as those who had a hospital discharge diagnosis from any of the above sources, or two Medicare outpatient claims that occurred at least one week apart, with *ICD-9-CM* codes of 441.3 or 441.4, or procedure codes of 38.44 or 39.71, or the following cause of death codes: *ICD-9* 441.3 or 441.4 or *ICD-10* code I71.3 or I71.4. AAAs based on procedure codes were required to be verified by diagnosis codes. Explanation of codes can be found elsewhere.[6] Some of these clinical diagnoses would include asymptomatic AAAs that were medically documented. We treated thoracic, thoracoabdominal, or unspecified aortic aneurysms as non-events.

To identify additional asymptomatic AAAs in the surviving ARIC cohort, we performed an abdominal ultrasound scan at the ARIC Visit 5 examination in 2011-2013. A radiologist with special vascular imaging expertise and an ultrasound technician specializing in vascular imaging centrally trained experienced cardiac ultrasonographers from each ARIC site in the technique of abdominal aortic scanning. After certification, the site sonographers followed the following scanning algorithm for each patient using a Philips iE33 high resolution duplex scanner and a Philips C5-1 transducer (Philips Healthcare, Bothell, WA):

1) Initially scan in both the transverse and longitudinal views to get an overall view of the aorta and its course, especially since the aorta can be quite tortuous. Identify the celiac and superior mesenteric arteries and the aortic bifurcation to set the boundaries of the abdominal aorta. Identify the renal arteries. Be sure that the aorta is imaged in a plane that is truly transverse to the aorta.

2) Measure from the outer edge of the wall of the aorta directly across the largest anterior-posterior (AP) (front to back) or transverse (side to side) diameter to the outer edge of the wall on the opposite side. If an oblique diameter is larger than either the AP or transverse diameter, record that as well.

3) Record on transverse imaging the AP and transverse diameters of the abdominal aorta at the following 4 levels:

a. Proximal Aorta: Immediately below the superior mesenteric artery.
b. Mid Aorta: In the region 2 cm inferior to the lower of the two primary renal arteries.
c. Distal Aorta: In the region 1 cm superior to the bifurcation.
d. In the region of the largest transverse diameter if it is different than one of the 3 measurements above.
e. If there is a potential AAA (i.e. any segment that is >2.8 cm), measure the maximal diameter in the AP and transverse dimensions. In addition, obtain a longitudinal view and measure both the maximal AP diameter and the total length of the aneurysm from top to bottom.

4) On the longitudinal view, demonstrate clearly the relationship of the top of the potential AAA to the renal arteries, so that it is clear whether the aneurysm begins above, at, or below the renal arteries.

5) If other arterial pathology is seen, such as intraluminal thrombus, saccular aneurysms, dissection or ulceration, carefully demonstrate its extent on longitudinal and transverse images.

Vascular imaging physicians over-read all images in any participant on whom the sonographer recorded a diameter measurement ≥ 2.8 cm, or in whom any possible vascular or non-vascular pathology was identified. In addition, as a quality control measure, the vascular imaging physicians reviewed a random sample of 5% of the remaining cohort. A participant was diagnosed as having an AAA if any infrarenal diameter measurement was $\geq$ 3 cm,[7] which defined asymptomatic AAA in our study. Of the 10,036 ARIC participants still alive through August 2013, 6,538 (65%) had a home or clinic ARIC examination and, of these, 5,911 (59% of the 10,036) had interpretable abdominal aortic ultrasonograms.

Data Analysis

We treated Visit 1 as baseline for the analysis for all risk factors but longitudinal smoking, for which baseline was Visit 4 or 3.

Analysis of clinical AAAs: We applied the following exclusions to the 15,792 ARIC participants from Visit 1: race other than white or African American (*n* = 48), prior AAA surgery (*n* = 11), and uncertain AAA status during follow-up (*n* = 30), resulting in 15,703 at risk of AAA from Visit 1. For the analysis of longitudinal smoking status, we further excluded 2,535 participants who were missing longitudinal smoking information and 75 participants who were diagnosed with AAA before Visits 4 or 3 (depending on the availability of smoking information at Visit 4). We calculated the length of follow-up as the time elapsed from the baseline to the first clinical AAA event, date of death, date of last contact (if lost), or through December 31, 2011. We computed incidence rates of clinical AAA stratified by demographic and cardiovascular risk factors and adjusted for age, race, and sex using Poisson regression models. Continuous risk factors were grouped into tertiles based on their overall distributions.

Calculation of lifetime risk for AAA: Lifetime risk of AAA was approximated as the cumulative incidence of clinical AAA from index age 45 years through age 85 (unless noted otherwise). Participants who died from causes other than AAA are no longer at risk for AAA. Thus, we used a modified life-table approach by Beiser et al[8] to estimate remaining lifetime risk for AAA to selected index ages and adjust for the competing risk of death. This method is similar to Kaplan-Meier analysis, except that death from another cause is not censored but is treated as another type of event. Thus, each participant was classified as either an AAA event, censored (loss to follow-up or the end of follow-up), or a non-AAA-related death, whichever came first. We used the Practical Incidence Estimators SAS Macro[8] to estimate the lifetime risk of clinical AAA in the entire cohort as well as subgroups defined by age, sex, race at baseline as well as longitudinal smoking status. For longitudinal smoking status, the index age started at 55 years until the maximum age of 80 years to ensure sufficient follow-up time and sample size.

Risk factor associations for clinical AAA: Cox Proportional hazards regression was performed to obtain hazard ratios of incident, clinical AAA associated with risk factors in nested multivariate models. Model 1 adjusted for age, race, and sex. We further adjusted for the following risk factors in Model 2 based on literature or the results of Model 1: height, pack-years of smoking, alcohol consumption (g/day), HDL-C, LDL-C, triglycerides, hypertension, PAD, and diabetes; for total cholesterol and smoking status as risk factors, to avoid collinearity, Model 2 did not include LDL-C or smoking pack-years, respectively. We tested for trend in hazard ratios across tertiles or groups using an ordinal variable designating each tertile/group. The proportional hazards assumption was evaluated by testing for interaction between each risk factor and log survival time and found that the assumption was not violated for most risk factors, with the exception of age and smoking pack-years ($p<0.01$). Therefore, we performed separate analyses for these two risk factors for the first 10 years of follow-up and for >10 years of follow-up, as the assumption held for each period separately.

Risk factor associations for ultrasound AAA: From 5,911 ARIC participants with usable ultrasounds obtained from ARIC Visit 5 in 2011-2013, we excluded participants who were not white or African American (*n* = 38) and those diagnosed with a clinical AAA before Visit 5 (*n* = 95), resulting in 5,778 participants, in whom we identified 75 asymptomatic AAAs for the analysis of Visit 1 risk factors. There were 4,853 participants (66 AAAs) included in the analysis of longitudinal smoking status. To adjust for the potential selection bias caused by differential participation in the 2011-2013 exam, we used inverse probability of attrition weighting (IPAW).[9] Briefly, for each participant we calculated weights based on the product of the probability of being alive at Visit 5 and the probability of having an abdominal ultrasound conditional on being alive given demographic and cardiovascular risk factors measured at Visit 1 and during follow-up.[6] We obtained odds ratios and 95% confidence intervals from IPAW general estimating

equation models using a logit link and robust standard errors,[9] which incorporated the added uncertainty of the weights in the models.

We used SAS Version 9.3 (SAS Institute, Inc., Cary, NC) in all of the analyses.

References

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